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SHORT COMMUNICATION

Sex-specific bimodal clustering of left ventricular ejection fraction in patients with acute heart failure

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Abstract

Aims There is an ongoing discussion whether the categorization of patients with heart failure according to left ventricular ejection fraction (LVEF) is scientifically justified and clinically relevant. Major efforts are directed towards the identification of appropriate cut-off values to correctly allocate heart failure-specific pharmacotherapy. Alternatively, an LVEF continuum without definite subgroups is discussed. This study aimed to evaluate the natural distribution of LVEF in patients presenting with acutely decompensated heart failure and to identify potential subgroups of LVEF in male and female patients.

Methods and results We identified 470 patients (mean age 75 ± 11 years, *n* = 137 female) hospitalized for acute heart failure in whom LVEF could be quantified by Simpson's method in an in-hospital echocardiogram. Non-parametric modelling revealed a bimodal shape of the LVEF distribution. Parametric modelling identified two clusters suggesting two LVEF peaks with mean (variance) of 61% (9%) and 31% (10%), respectively. Sub-differentiation by sex revealed a sex-specific bimodal clustering of LVEF. The respective threshold differentiating between 'high' and 'low' LVEF was 45% in men and 52% in women.

Conclusions In patients presenting with acute heart failure, LVEF clustered in two subgroups and exhibited profound sex-specific distributional differences. These findings might enrich the scientific process to identify distinct subgroups of heart failure patients, which might each benefit from respectively tailored (pharmaco)therapies.

Keywords Heart failure; Left ventricular ejection fraction; Sex differences

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Background

The current classification of heart failure (HF) is based on left ventricular ejection fraction (LVEF).[1,2] Originally, thresholds defining reduced LVEF (i.e. ≤40%) and preserved LVEF (i.e. >50%) were chosen by trialists to facilitate the identification of distinct patient groups. Over the last decades, these thresholds and patient categories have been firmly integrated into the clinical and scientific perception of the HF syndrome.[2] Recently, this view has been challenged by arguing for continuity of the LVEF distribution across the HF spectrum.[3] Of note, currently used LVEF thresholds have never been formally derived from data.

Aims

We aimed to evaluate the natural distribution of LVEF in patients presenting with acute HF and investigate potential sex-specific differences.

Methods

As part of a larger programme at our hospital aiming to prospectively identify patients with HF, we analysed those admitted for acute HF. Exclusion criteria were cardiogenic

shock, high-output HF, or awaiting urgent heart transplantation. The current analysis was restricted to patients providing interpretable echocardiograms allowing to derive LVEF by Simpson's method. LVEF was extracted from the clinical report by automated information extraction.[4]

We first estimated the distribution of LVEF using a histogram estimator. Bin width was selected by minimizing the cross-validated empirical risk.[5] In addition, the distribution was estimated using a kernel density estimator. Bandwidth was selected by robust biased cross-validation.[6] In a latent class analysis, we then fitted parametric Gaussian mixture models,[7] with an increasing number of components to identify meaningful subgroups. To determine the optimal number of Gaussian components, the Bayesian information criterion (BIC) was calculated. The BIC is considered a conservative criterion; its minimum defines the optimal number of components. Finally, the optimal model was determined and plotted vs. the non-parametric distribution estimates. This process was repeated for male and female patients separately. Data were analysed using *R* (Version 3.5.2, Foundation for Statistical Computing, Vienna, Austria) with the *flexmix* (Version 2.3-15) package for Gaussian mixture modelling. Further details on the analytical approach are described in the Supporting Information. To compare outcomes, length of hospitalization and the 6 month risk for all-cause death, cardiac death, and the number of rehospitalizations were ascertained. The study was conducted according to Good Clinical Practice, and all study participants provided written informed consent.

Results

Four hundred and seventy patients entered the current analysis. Their mean age was 75 ± 11 years, and 137 (29%) were female. Characteristics of the whole sample are provided in *Table 1*. For the histogram estimator, the optimal number of bins was determined at 11 bins, with a minimal empirical risk of −1.68% (*Figure 1A*). The bandwidth of the kernel density estimator was calculated as 3.69. *Figure 1B* shows the resulting distribution estimates. The estimated distribution of LVEF clearly identified two clusters, that is, a bimodal shape.

The minimal BIC approach also suggested two components (*Figure 2A*). In the two-component model, mean (variance) values, that is, peaks for LVEF, were 61% (9%) and 31% (10%), with both components covering 61% and 44% of patients, respectively (*Figure 2D*). BIC analysis by sex (for men, see *Figure 2B* and *2E*; for women, see *Figure 2C* and *2F*) confirmed two components for each sex. The respective means (variances) for the LVEF in male patients were 59% (8%) and 30% (9%) and were 65% (8%) and 36% (13%) in female patients. Cut points to separate patient subgroups were set at the intersection of the component distribution curves, that is, where the point probability of being attributed to either cluster is equal. In the total sample, the two-component model suggested a cut point of 46% to categorize patients into low and high LVEF regardless of sex. The sex-specific cut points were 45% for male and 52% for female patients. Accordingly, the prevalence for high LVEF and low LVEF in men was 59% and 48% and was 68% and 43% in women, respectively.

Table 1 Patient characteristics by identified clusters of LVEF

Variable	All patients (N = 470)	'Low LVEF' (LVEF < 46%) (N = 206)	'High LVEF' (LVEF ≥ 46%) (N = 264)
Age (years), mean (SD)	74.7 (11.1)	71.8 (12.5)	77.1 (9.2)
Female sex, *n* (%)	173 (36.8)	61 (29.6)	112 (42.4)
Type of heart failure, *n* (%)			
Chronic	404 (86.0)	181 (87.9)	223 (84.5)
De novo	65 (13.8)	25 (12.1)	41 (15.5)
BMI at discharge (kg/m^2), mean (SD)	27.9 (5.9)	27.3 (4.9)	28.4 (6.5)
Hypertension, *n* (%)	435 (92.6)	188 (91.3)	247 (93.6)
Diabetes, *n* (%)	236 (50.2)	110 (53.4)	126 (47.7)
History of coronary artery disease, *n* (%)	189 (40.2)	97 (47.1)	92 (34.9)
eGFR (mL/min/1.73 m^2), median (quartiles)			
At admission	48 (33, 64)	47 (32, 63)	48 (33, 64)
At discharge	46 (32, 59)	47 (32, 58)	44 (32, 61)
NT-proBNP (pg/mL)			
At admission	4523 (2148, 10 019)	6706 (3599, 14 038)	3375 (1459, 6622)
At discharge	2132 (979, 5176)	3022 (1497, 7639)	1604 (737, 3728)
Length of hospital stay (days), mean (SD)	11.6 (7.6)	12.7 (8.1)	10.8 (7.2)
Events within 6 months after discharge			
Death, *n* (%)	72 (15.3)	31 (15.1)	41 (15.5)
Cardiac death, *n* (%)	32 (6.8)	18 (8.7)	14 (5.3)
Rehospitalizations (*n*), mean (SD)	1.78 (1.12)	1.79 (1.15)	1.77 (1.09)

BMI, body mass index; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation.

Figure 1 Derivation of left ventricular ejection fraction (LVEF) clusters measured at discharge, in patients admitted for acute heart failure. (A) Empirical loss per histogram bin in the range between 1 and 23. Blue line denotes smoothed curve with standard error in grey. (B) Histogram density estimate with the optimal number of bins (n = 11) and kernel density estimator with bandwidth selection using biased cross-validation.

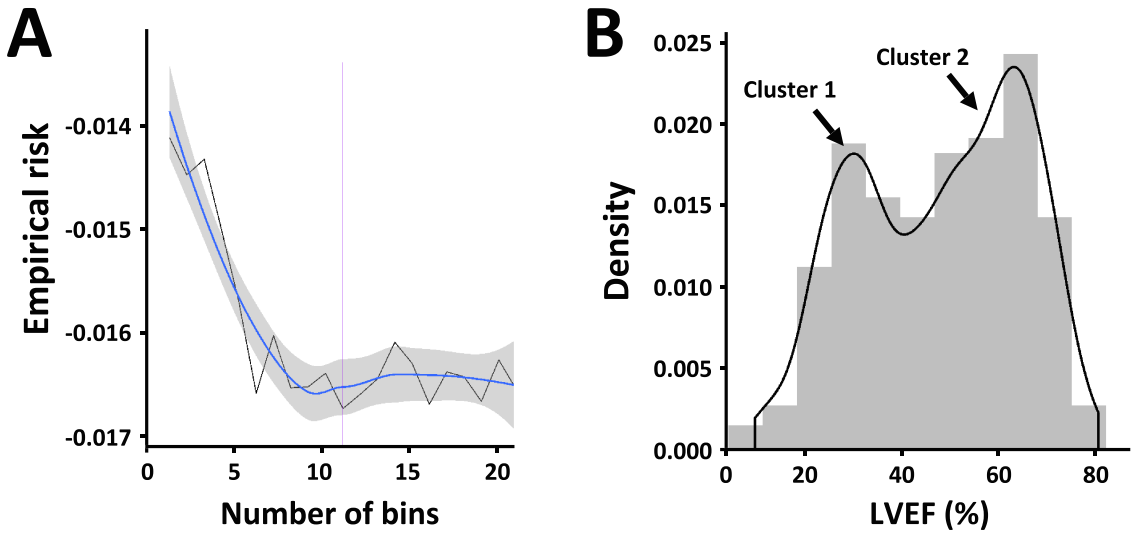
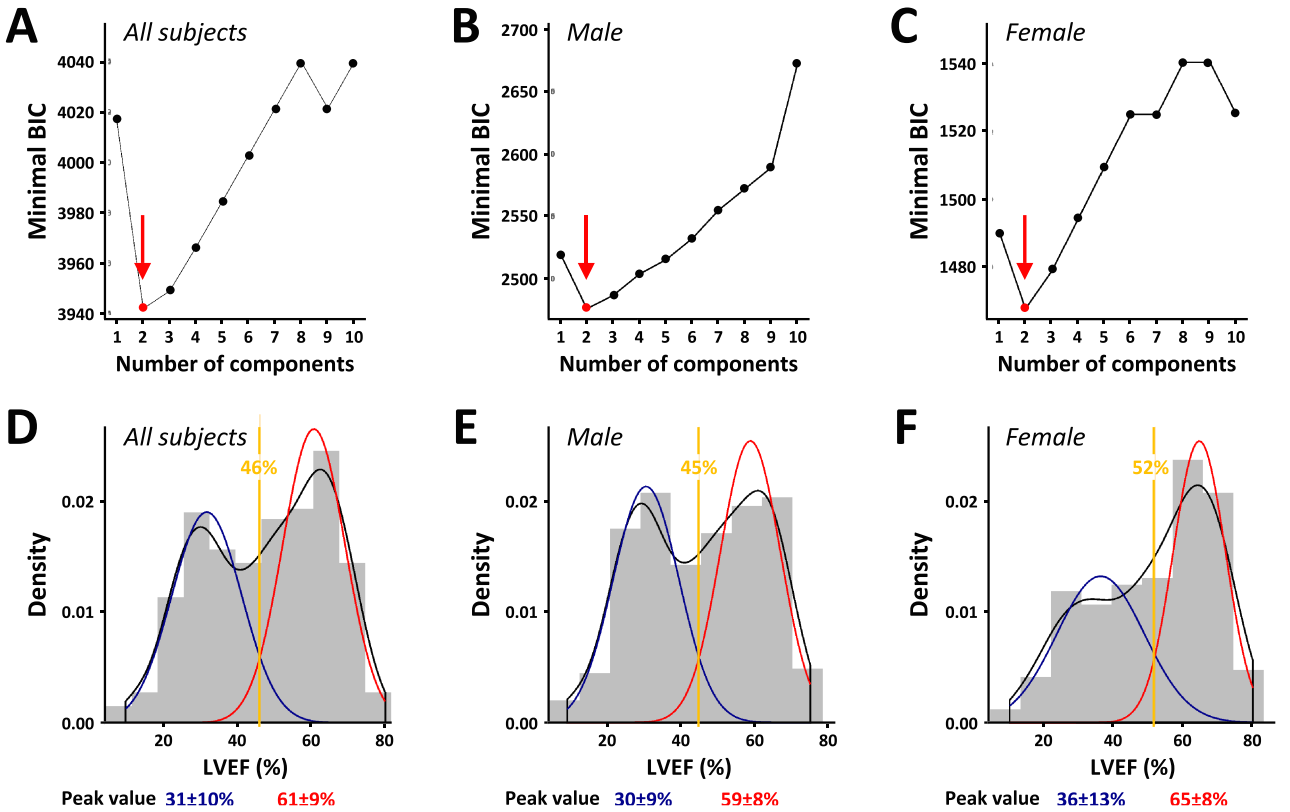


Figure 2 Empirical derivation of left ventricular ejection fraction (LVEF) peaks and thresholds using the *Bayesian information criterion* (BIC), in patients admitted for acute heart failure. The minimal BIC indicates the optimal number of components. (A–C) Minimal BIC per number of components (each derived from 50 repeated model fits) in the overall, male, and female population. (D–F) Respective two-component models in all subjects, men, and women, as determined per BIC. Orange lines indicate LVEF cut-off determined from parametric models. SD, standard deviation.



Characteristics of the LVEF subgroups identified by latent class analysis are further described in *Table 1*. Patients with high LVEF were older and more often female and exhibited lower N-terminal pro-brain natriuretic peptide levels. Length of hospital stay was 2 days shorter in patients with high LVEF, but their 6 month prognosis was similar compared with patients with low LVEF.

Conclusions

In patients hospitalized for decompensated HF, quantitatively determined LVEF clustered in a bimodal fashion when applying an unbiased approach employing non-parametric methods. Subsequent parametric modelling using the BIC method confirmed two components, both in the overall sample and in sex-specific subgroups. To the best of our knowledge, this report is the first to apply latent class analysis allowing unbiased modelling of the natural LVEF distribution in unselected patients, but it concurs with an earlier report from the CHARM trial programme.[8] The threshold of 46% separating low and high LVEF in the total sample was 6% above the empirically derived threshold of 40% for patients with 'HF with reduced LVEF' and well within the range for 'HF with mid-range LVEF'.[2] Of note, the prevalence of higher LVEF was larger for both sexes. Although coronary artery disease was expectedly somewhat more frequent in patients with low LVEF, the co-morbidity profiles of both subgroups were surprisingly similar, as was prognosis. Of note, sex-dependent differences were also reported for coronary heart disease.[9]

Sex-specific analyses indicated that cut points for men and women differentiating between high and low LVEF were decisively different, that is, 45% vs. 52%. The magnitude of this 7-point difference must be considered large with respect to measurement error, and it is clinically relevant. It suggests that LVEF in HF mandates a sex-specific context for interpretation. It could partially explain why the LVEF threshold associated with a clinical benefit in the recent PARAGON-HF trial was higher in women than in men.[10] Although LVEF is only one out of many functional descriptors of HF,[1,3] our findings may trigger further research into the sex-specific response to common stimuli that characterize HF's underlying aetiology in an individual patient. Our findings await external validation in other samples of patients with acute HF.

Conflict of interest

C.H. and N.S. have nothing to declare. C.M. reports research cooperation with the University of Würzburg and TOMTEC Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany; advisory and speaker honoraria as well as travel grants from Amgen, TOMTEC, Orion Pharma, Alnylam, Akcea, Pfizer, Boehringer Ingelheim, and EBR Systems; principal investigation in trials sponsored by Alnylam and AstraZeneca; and financial support from the interdisciplinary centre for clinical research—IZKF Würzburg (advanced clinician–scientist programme). F.S. receives financial support from the Interdisciplinary Center for Clinical Research (IZKF) of the Medical Faculty, University of Würzburg (MD/PhD programme scholarship). S.F. reports advisory and speaker honoraria as well as travel grants from Amgen Europe, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol Myers Squibb GmbH, Daiichi Sankyo, MSD, Novartis, Pfizer, Sanofi, Servier, and Vifor. G.E. reports significant honoraria for trial leadership from Abbott and Novartis; has been a consultant for Abbott, Boehringer Ingelheim, Novartis, ResMed, and Vifor (modest); and received significant grant support from Boehringer Ingelheim, Thermo Fisher, Siemens Healthineers, Vifor, and Federal Ministry of Education and Research. C.E.A. reports honoraria for trial leadership from Abbott, Boehringer Ingelheim, and Novartis; has been a consultant for and/or received speaker honoraria from Abbott, Boehringer Ingelheim, Novartis, ResMed, Springer, and Vifor; and received grant support from Boehringer Ingelheim, Thermo Fisher, Siemens Healthineers, Vifor, and German Federal Ministry of Education and Research. S.S. reports research grants from the German Ministry of Education and Research, European Union, and University Hospital Würzburg; participation in data safety monitoring or event adjudication in studies sponsored by Roche and Medtronic; participation in advisory boards for Novartis, Bayer, Boehringer Ingelheim, Thermo Fisher, and Boston Scientific; principal investigation in trials (co-)sponsored by Boehringer Ingelheim, Novartis, Bayer, and Lundbeck; and speaker honoraria by Boehringer Ingelheim, Servier, Novartis, AstraZeneca, Pfizer, Bayer, and Thermo Fisher, outside the submitted work.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information.

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